Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

Table 15f. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Insulin Resistance, Asymptomatic Hyperglycemia, Diabetes Mellitus (Last updated April 14, 2020; last reviewed April 14, 2020)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Insulin Resistance, Asymptomatic Hyperglycemia, DM[a]	ZDV, LPV/r, and possibly other PIs	**Onset:** • Weeks to months after beginning therapy **Presentation:** • Asymptomatic fasting hyperglycemia (which sometimes occurs in the setting of lipodystrophy), metabolic syndrome, or growth delay • Symptomatic DM (rare)	**Children:** • Insulin resistance, 6% to 12% (incidence is higher during puberty, 20% to 30%) • Impaired fasting glucose, 0% to 7% • Impaired glucose tolerance, 3% to 4% • DM, 0.2 per 100 child-years	**Risk Factors for Type 2 DM:** • Lipo-dystrophy • Metabolic syndrome • Family history of DM • High BMI (obesity)	**Prevention:** • Lifestyle modification **Monitoring:** • Monitor for signs of DM, change in body habitus, and acanthosis nigricans. • Obtain RPG levels at initiation of ART, 3–6 months after ART initiation, and yearly thereafter. • In patients with an RPG ≥140 mg/dL, obtain FPG after an 8-hour fast and consider referring the patient to an endocrinologist.	Counsel patient on lifestyle modification (e.g., implementing a diet low in saturated fat, cholesterol, trans fat, and refined sugars; increasing physical activity; ceasing smoking). Recommend that the patient consult with a dietician. If the patient is receiving ZDV, switch to TAF, TDF, or ABC. **For Patients with Either an RPG ≥200 mg/dL Plus Symptoms of DM or an FPG ≥126 mg/dL:** • These patients meet diagnostic criteria for DM; consult an endocrinologist. **For Patients with an FPG of 100–125 mg/dL:** • Impaired FPG suggests insulin resistance; consult an endocrinologist. **For Patients with an FPG <100 mg/dL:** • This FPG is normal, but a normal FPG does not exclude insulin resistance. Recheck FPG in 6–12 months.

[a] Insulin resistance, asymptomatic hyperglycemia, and DM form a spectrum of increasing severity.

Insulin Resistance: Often defined as elevated insulin levels for the level of glucose observed.

Impaired FPG: Often defined as an FPG of 100–125 mg/dL.

Impaired Glucose Tolerance: Often defined as an elevated 2-hour PG of 140–199 mg/dL in a 75-g OGTT (or, if the patient weighs <43 kg, 1.75 g per kg of glucose up to a maximum of 75 g).

DM: Often defined as either an FPG ≥126 mg/dL, an RPG ≥200 mg/dL in a patient with hyperglycemia symptoms, an HgbA1c of ≥6.5%, or a 2-hour PG ≥200 mg/dL in an OGTT.

However, the Panel does not recommend performing routine measurements of insulin levels, HgbA1c, or glucose tolerance without consulting an endocrinologist. These guidelines are instead based on the readily available RPG and FPG levels.

Key: ABC = abacavir; ARV = antiretroviral; BMI = body mass index; dL = deciliter; DM = diabetes mellitus; FPG = fasting plasma glucose; HgbA1c = glycosylated hemoglobin; LPV/r = lopinavir/ritonavir; OGTT = oral glucose tolerance test; the Panel = Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV; PG = plasma glucose; PI = protease inhibitor; RPG = random plasma glucose; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

References

1. Aldrovandi GM, Lindsey JC, Jacobson DL, et al. Morphologic and metabolic abnormalities in vertically HIV-infected children and youth. *AIDS*. 2009;23(6):661-672. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19279441.

2. American Diabetes Association. Classification and diagnosis of diabetes. *Diabetes Care*. 2016;39 Suppl 1:S13-22. Available at: http://www.ncbi.nlm.nih.gov/

pubmed/26696675.

3. Chantry CJ, Hughes MD, Alvero C, et al. Lipid and glucose alterations in HIV-infected children beginning or changing antiretroviral therapy. *Pediatrics.* 2008;122(1):e129-138. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18519448.

4. Dirajlal-Fargo S, Musiime V, Cook A, et al. Insulin resistance and markers of inflammation in HIV-infected Ugandan children in the CHAPAS-3 Trial. *Pediatr Infect Dis J.* 2017;36(8):761-767. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28067719.

5. Espiau M, Yeste D, Noguera-Julian A, et al. Metabolic syndrome in children and adolescents living with HIV. *Pediatr Infect Dis J.* 2016;35(6):e171-176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26910591.

6. Fortuny C, Deya-Martinez A, Chiappini E, Galli L, de Martino M, Noguera-Julian A. Metabolic and renal adverse effects of antiretroviral therapy in HIV-infected children and adolescents. *Pediatr Infect Dis J.* 2015;34(5 Suppl 1):S36-43. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25629891.

7. Geffner ME, Patel K, Miller TL, et al. Factors associated with insulin resistance among children and adolescents perinatally infected with HIV-1 in the pediatric HIV/AIDS cohort study. *Horm Res Paediatr.* 2011;76(6):386-391. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22042056.

8. Hadigan C, Kattakuzhy S. Diabetes mellitus type 2 and abnormal glucose metabolism in the setting of human immunodeficiency virus. *Endocrinol Metab Clin North Am.* 2014;43(3):685-696. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25169561.

9. Hazra R, Hance LF, Monteiro JP, et al. Insulin resistance and glucose and lipid concentrations in a cohort of perinatally HIV-infected Latin American children. *Pediatr Infect Dis J.* 2013;32(7):757-759. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23360832.

10. Innes S, Abdullah KL, Haubrich R, Cotton MF, Browne SH. High prevalence of dyslipidemia and insulin resistance in HIV-infected pre-pubertal African children on antiretroviral therapy. *Pediatr Infect Dis J.* 2016;35(1):e1-7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26421804.

11. Loomba-Albrecht LA, Bregman T, Chantry CJ. Endocrinopathies in children infected with human immunodeficiency virus. *Endocrinol Metab Clin North Am.* 2014;43(3):807-828. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25169569.

12. Mirani G, Williams PL, Chernoff M, et al. Changing trends in complications and mortality rates among US youth and young adults with HIV infection in the era of combination antiretroviral therapy. *Clin Infect Dis.* 2015;61(12):1850-1861. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26270680.

13. Non LR, Escota GV, Powderly WG. HIV and its relationship to insulin resistance and lipid abnormalities. *Transl Res.* 2017;183:41-56. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28068521.

14. Paganella MP, Cohen RA, Harris DR, et al. Association of dyslipidemia and glucose abnormalities with antiretroviral treatment in a cohort of HIV-infected Latin American children. *J Acquir Immune Defic Syndr.* 2017;74(1):e1-e8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27570910.

15. Patel K, Wang J, Jacobson DL, et al. Aggregate risk of cardiovascular disease among adolescents perinatally infected with the human immunodeficiency virus. *Circulation.* 2014;129(11):1204-1212. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24366631.

16. Samaras K. Prevalence and pathogenesis of diabetes mellitus in HIV-1 infection treated with combined antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2009;50(5):499-505. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19223782.

17. Takemoto JK, Miller TL, Wang J, et al. Insulin resistance in HIV-infected youth is associated with decreased mitochondrial respiration. *AIDS.* 2017;31(1):15-23. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27755108.

18. Geffner ME, Patel K, Jacobson DL, et al. Changes in insulin sensitivity over time and associated factors in HIV-infected adolescents. *AIDS.* 2018;32(5):613-622. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29280758.